REMARKS

Claims 51, 65, 88, and 94 have been amended to correct a minor informality. Claims 85-90, 93-95, and 100-103 have been canceled. New claim 105 is supported by claims 51 and 64. New claim 106 is supported by claim 51 and the specification, for example at page 29, lines 5-10. Claims 51-52, 55-56, 59-60, 62, 64, 91, 96-97, and 105-106 are currently active and under consideration.

Virulence and pathogenicity of microorganisms is often enhanced when growing as a biofilm. For example, most cystic fibrosis (CF) patients suffer from recurrent and chronic end-bronchial *Pseudomonas aeruginosa* infections. An inflammatory response occurs resulting in a shift of the organism's phenotype from non-mucoid to a mucoid phenotype. This phenotype grows an endo-bronchial biofilm, which is impossible to eradicate through conventional antibiotic therapy (page 6, lines 23-28 of WO2004/062677, the PCT publication of the present application).

The present invention provides a novel, alternative approach for tackling microbial infections within a biofilm with a composition comprising a bacteriophage and a first polysaccharide lyase enzyme (*Id.*, page 7, lines 1-3). The bacteriophage preferably targets one or more bacteria of the biofilm (*Id.*, page 8, line 32), and the polysaccharide lyase enzyme breaks down a component of the biofilm, for example alginate produced by mucoid strains of *P. aeruginosa* (*Id.*, page 10, lines 10-18). A pharmaceutically-acceptable agent, for instance an antibiotic (*Id.*, page 12, lines 15-24), is also present in the composition.

The rejection of claims under 35 U.S.C. §§ 102(b) and 103(a) over Hughes *et al.* (Bioline, pages 325-331, 2001), or over Hughes *et al.* in view of Wilde *et al.* (WO 89/11291), Nairn (Remington, The science and practice of pharmacy, Vol. II, 1995, pages 1495-1523) or Budny *et al.* (U.S. Pat. Application Publication, US 2002/0037260) is respectfully traversed. None of the applied references describes or identifies a phage carrying and encoding hydrolytic enzymes.

The Office is of the opinion that

> Hughes *et al.* teach that application of phage carrying and encoding hydrolytic enzymes (alginate lyase) offers huge therapeutic benefits [...]

(Office Action of January 13, 2009, page 6, third paragraph).

Hughes *et al.* reviews the history of bacteriophage therapy in the fight to control bacterial infections (Hughes *et al.*, page 325, first paragraph). The reference focuses on the formation of bacterial colonies in the mucus of the lungs of CF patients, which leads to chronical infections difficult to eradicate. In particular, poor clearance of *P. aeruginosa* from the lungs has been found to be partly due to the phenotypic conversion of *P. aeruginosa* from a non-mucoid to a mucoid form which is associated with the production of virulence factors. *P. aeruginosa* is then able to persist in micro-colonies embedded in a biofilm of alginate in several parts of the endo-bronchial tree (*Id.*, page 327, last paragraph).

The authors of Hughes *et al.* then cite references examining the interaction of bacteriophages with biofilms (*Id.*, page 328, first paragraph), including one reporting a bacteriophage able to infect the biofilm forming bacterium *Enterobacter agglomerans 53b*, where the bacteriophage was shown to possess a depolymerase specific for the exopolysaccharide in the biofilm of the bacterium (*Id.*, page 328, last paragraph). Also cited is a report that *P. aeruginosa* phage is able to diffuse through alginate gels of *P. aeruginosa*, and alginate treated with phage has a lower molecular weight than untreated alginate. The authors conclude that the evidence indicated that the bacteriophage were responsible for facilitating a reduction of the biofilm through enzymic degradation and that the bacterial host may be the source of the enzyme (*Id.*, page 329, first paragraph).

Based on the above evidence, Hughes *et al.* sets forth the therapeutic goal of treating *P. aeruginosa* infections, refractory to conventional therapy owing to the development of biofilms, by the application of phage carrying and encoding hydrolytic enzymes to destroy alginate biofilms and the eradication of *P. aeruginosa* infection (*Id.*, page 329, second paragraph).

Hughes *et al.* does not describe or identify a phage carrying and encoding hydrolytic enzymes, but merely sets forth the desirability to obtain such a phage as a therapeutic goal, *i.e.* just an invitation to investigate. The reference does not identify or describe any *P. aeruginosa* phage carrying and encoding hydrolytic enzymes. Rather, it merely suggests treating infections with such a phage, without actually providing the

phage or guidance as to how make it. As such, Hughes *et al.* provides nothing more than an invitation to further experimentation; there is therefore no adequate basis in fact to reasonably support the determination that Hughes *et al.* discloses a phage encoding and carrying an enzyme such as alginate lyase. An invitation to investigate is not an inherent disclosure (MPEP § 2112 (IV), citing *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference [...] must be examined to see if [it] merely invites further experimentation to find the species).

This lack of an adequate factual basis is not cured by the other applied references. Wilde *et al.* teaches granulocyte-derived polypeptides similar to defensins (Wilde *et al.*, page 2, line 27 to page 3, line 7), but is silent as to *P. aeruginosa* phages. Nairn teaches the preparation of solutions, emulsions, suspensions and extracts, including metered dose inhalers (MDIs) for delivering metered doses of a drug to the respiratory tract (Nairn, page 1508, first column, second paragraph), but the authors do not disclose *P. aeruginosa* phages.

Budny *et al.* teaches a composition for treating a biofilm structure comprising two "enzyme-anchor" components. The enzyme of the first enzyme-anchor component is selected for its ability to degrade the biofilm structure; the enzyme of the second component is selected for its ability to act directly on bacteria for a bactericidal effect (Budny *et al.*, paragraph [0016]). The "anchors" can be agents or molecular species known to have an affinity for the biofilm or the surfaces near the biofilm or known binding domains (*Id.*, paragraph [0034]). For degrading biofilms of *P. aeruginosa*, alginate lyase from bacterial sources is suggested (*Id.*, paragraphs [0126] - [0127]). No phages coding and carrying hydrolytic enzymes is identified or described, however.

In view of the foregoing, none of the applied references describes or identifies a phage carrying and encoding hydrolytic enzymes. Withdrawal of the rejections is therefore respectfully submitted.

In response to the rejection under 35 U.S.C. § 112, first paragraph, Applicants submit that the relevant deposits under the terms of the Budapest Treaty have been made. Applicants further undertake that the deposited materials will be irrevocably and without restriction released to the public upon the issuance of a patent.

It is submitted that the present application is now in condition for allowance. Early notice of such action is respectfully requested.

Respectfully submitted,

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